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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,375	12/08/2003	Philip J. Barr	368292001700	4368

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EXAMINER

KIM, JENNIFER M

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/731,375

Applicant(s)

BARR ET AL.

Examiner

Jennifer Kim

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5,8,11 and 13-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5,8,11 and 13-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/6/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment filed October 6, 2006 have been received and entered into the application.

Action Summary

The objection of claim 19 under 37 CFR 1.75(c), made in the previous Office Action is hereby expressly withdrawn in view of Applicant's amendment.

The rejection of claims 20 and 21 under 35 U.S.C. 112, second paragraph is hereby expressly withdrawn in view of Applicant's amendment.

The rejection of claims 5, 8, 11 and 13-21 under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) in view of Grote et al. (U.S. Patent No. 6,670,327B1) of record and further in view of Brake et al. (U.S. Patent No. 4,752,576) are hereby expressly withdrawn in view of Applicant's amendment.

Applicants' amendment necessitated new grounds of rejection presented in this Office action as follows.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 8, 11, 13 and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) of record in view of Lezdey et al. (U.S. Patent No. 6,174,859 B1).

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Avidano et al. teach otorrhea samples were collected from **human patients with otitis media** and a **perforated tympanic membrane** and the samples were treated with ilomostat plus **alpha1-antitrypsin** *in vitro*. (abstract). A statistically significant ($p < 0.05$) decrease in protease activity against **Pseudomonas** was seen **with the addition of alpha 1-antitrypsin** or **ilomostat plus alpha1-antitrypsin** but not with ilomostat alone. (see Fig. 1, page 348). Avidano et al. teach that chronic otitis media is a common problem associated with a nonintact tympanic membrane involving **pseudomonas**. (abstract). Avidano et al. teach that the concentration of ilomostat was prepared with 800ug/ml (0.8mg/ml) in a vehicle and the alpha 1-antitrypsin was prepared at a concentration of 100ug/ml (0.1mg/ml). These amounts are within the nontoxic amounts claimed by the Applicants set forth in claims 18 and 19.

Avidano et al. do not teach the actual *vivo* treatment with an effective *vivo* amount set forth in claim 13 and further comprising steroid set forth in claim 5.

Lezdey et al. teaches composition comprising **alpha 1-antitrypsin** and **steroid** compound for the **patients (vivo)** suffering from **ear infections** caused by **pseudomonas**. (abstract, claims 1-16, particularly claims 1 and 16, Examples 1-8 particularly 7 and 8). Lezdey et al. teaches the effective amount of alpha 1-antitrypsin to be administered *in vivo* from about **0.1 to 20 mg per 1ml of solution**.

It would have been obvious to one of ordinary skill in the art to employ the teaching of Avidano et al. to a patient (*vivo*) suffering from otitis media and a perforated tympanic membrane by administering effective amount of alpha one-antitrypsin without significant ototoxicity because Avidano et al. obtained statistically significant decrease in

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protease activity against *Pseudomonas* in the sample collected from human who actually had otitis media and because the effective therapeutic amount of alpha one-antitrypsin for the treatment of ear infection caused by *pseudomonas* is well known by Lezdey et al. One would have been motivated to employ the successful teaching of Avidano et al. in vitro data comprising human sample of otitis media having perforated tympanic membrane to a patient actually suffering from the such condition in order to achieve an expected benefit of actual effect in vivo. One would have been motivated to make such modification because Avidano et al. obtained statistically significant decrease in protease activity in sample collected from human with otitis media. Further, to employ the result obtained from the actual human sample taught by Avidano et al. and modify further in vivo would be next logical step. Moreover, to further incorporate an effective amount of steroid in the obvious method, such is obvious because Lezdey et al. teaches that steroids are routinely combined with **alpha 1-antitrypsin** for the **patients (vivo)** suffering from **ear infections** caused by **pseudomonas**. One would have been motivated to combine steroid with alpha one-antitrypsin in order to achieve at least an additive effect in treatment of ear infection involved with *pseudomonas* with the routine combination therapy well known by Lezdey et al. With regard to the cause of perforated tympanic membrane due to tympanostomy set forth in claim 8, such is obvious because the alpha one-antitrypsin is effective for the treatment of otitis media with perforated tympanic membrane regardless of its etiology. Absent any evidence to contrary, there would have been a reasonable expectation of successfully treating an individual having otitis media and a perforated tympanic membrane with alpha one-

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antitrypsin well known by Avidano et al. having significant antiprotease activity in human otitis media sample.

Claims 14, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) of record in view of Lezdey et al. (U.S. Patent No. 6,174,859 B1) as applied to claims 5, 8, 11 and 13 above, and further in view of Brake et al. (U.S. Patent No. 4,752,576) of record.

The teachings of Avidano et al, Lezdey et al as applied as before.

Avidano et al, and Lezdey et al. do not teach the source of the alpha-1 antitrypsin is yeast-expressed rAAT set forth in claim 14 and the result of the treatment set forth in claims 20 and 21.

Brake et al. teach a method for producing alpha1-antitrypsin (AAT) by recombinant methods from yeast. This method provides high level production of the protein. (abstract, column 1, lines 59-68, column 2, lines 7-15).

It would have been obvious to one of ordinary skill in the art to employ the recombinant AAT obtained by yeast –expressed rAAT in Avidano et al as modified by Lezdey et al. because Brake et al. teach the method of producing alpha1-antitrypsin (ATT) by recombinant methods in yeast provides high level production of the protein. One would have been motivated to employ yeast-expressed rAAT in Avidano et al's method modified by Lezdey et al. because the method of producing the alpha1-antitrypsin by yeast method provided high level of production and is well known and readily available by Brake et al. Further, to optimize different signs and symptoms to measure and detect an ototoxicity of a given treatment involving otitis media is well

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within the knowledge of the skilled artisan. Once the patient is being treated with a particular therapy involving a particular regimen, it is well within the knowledge of skilled artisan to routinely measure and evaluate the patient's condition and detect signs and symptoms of toxicity.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Response to Arguments

Applicants' arguments filed October 6, 2006 have been fully considered but they are not persuasive. Applicants argue that in order to establish a prima facie case of obviousness, the PTO must satisfy three requirements, first, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings; second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made; third, the prior art reference (or references when combined) must teach or suggest all the claimed limitations. This is

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not persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Applicant's claimed subject matter is clearly suggested and encompassed by the teachings of the prior art and in the knowledge generally available to one of ordinary skill in the art. Avidano et al. have performed vitro data and the samples used in the data obtained from the actual human suffering from otitis media with a nonintact tympanic membrane; Avidano et al. demonstrate that there is an advantage in the treatment by administration of alpha-1 antitrypsin with Ilomostat together by showing statistically significant decrease in protease activity. It is in the general knowledge that otitis media is treated topically administering active agents in external auditory canal to an individual having otitis media and this method is also well taught by Lezdey et al. in Example 6 that the antibiotics generally comprising alpha 1-antitrypsin with steroids are administered into an infected ear. It is the examiner's position that the claimed subject matter to employ Avidano et al's result to an individual suffering from otitis media with perforated tympanic membrane in order to achieve an expected benefit of significantly reduced protease activity thereby treating pseudomonas infection in the patients with otitis media. Further, this modified method provides the treatment without significant ototoxicity because the amounts of active agents in generally known in the prior art is

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within Applicant's claimed non-toxic amounts. Applicants argue that it could not be predicted whether AAT—or inhibitors of matrix metalloproteases, notably ilomostat, or ilomostat in combine with AAT—would prove sufficiently nonototoxic as to permit effective topical administration in the setting of a perforated tympanic membrane. This is not persuasive because Applicant's have provide no evidence why same active agents with the same amounts known in the art for the same treatment as claimed would provide different biological effect. (lack ototoxicity). The method of Avidano et al. as modified by Lezdey et al. would obviously give same result because the amount to be utilized are well-known and within the Applicant's claimed range. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

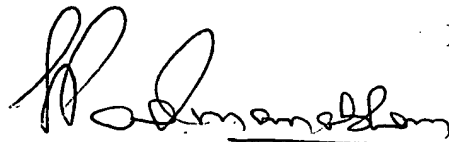
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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A handwritten signature in black ink, appearing to read 'S. Padmanabhan', written in a cursive style.

Sreenivasan Padmanabhan
Supervisory Primary Examiner
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Jmk

December 5, 2006